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Long-Term Therapy with Adefovir Dipivoxil for HBeAg-Negative Chronic Hepatitis B

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ABSTRACT

BACKGROUND

Treatment with adefovir dipivoxil for 48 weeks resulted in histologic, virologic, and biochemical improvement in patients with hepatitis B e antigen (HBeAg)–negative chronic hepatitis B. We evaluated the effect of continued therapy as compared with cessation of therapy.

METHODS

One hundred eighty-five HBeAg-negative patients with chronic hepatitis B were assigned to receive 10 mg of adefovir dipivoxil or placebo once daily for 48 weeks (ratio, 2:1). After week 48, patients receiving adefovir dipivoxil were again randomly assigned either to receive an additional 48 weeks of the drug or to switch to placebo. Patients originally assigned to placebo were switched to adefovir dipivoxil. Patients treated with adefovir dipivoxil during weeks 49 through 96 were subsequently offered continued therapy. The primary end points were changes in hepatitis B virus (HBV) DNA and alanine aminotransferase levels.

RESULTS

Treatment with adefovir dipivoxil resulted in a median decrease in serum HBV DNA of 3.47 log copies per milliliter (on a base-10 scale) at 96 weeks and 3.63 log copies per milliliter at 144 weeks. HBV DNA levels were less than 1000 copies per milliliter in 71 percent of patients at week 96 and 79 percent at week 144. In the majority of patients who were switched from adefovir dipivoxil to placebo, the benefit of treatment was lost (median change in HBV DNA levels from baseline, –1.09 log copies per milliliter; only 8 percent of patients had levels below 1000 copies per milliliter at week 96). Side effects during weeks 49 through 144 were similar to those during the initial 48 weeks. Resistance mutations rtN236T and rtA181V were identified in 5.9 percent of patients after 144 weeks.

CONCLUSIONS

In patients with HBeAg-negative chronic hepatitis B, the benefits achieved from 48 weeks of adefovir dipivoxil were lost when treatment was discontinued. In patients treated for 144 weeks, benefits were maintained, with infrequent emergence of viral resistance.

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An estimated 400 million people worldwide are chronically infected with hepatitis B virus (HBV). One million die each year from complications of infection, including cirrhosis, hepatocellular carcinoma, or both.[1] Hepatitis B e antigen (HBeAg)–negative chronic hepatitis B represents a late phase in the course of HBV infection.[2] Mutations in the precore promoter regions, core promoter regions, or both, which prevent the formation of HBeAg, are selected during or after HBeAg loss and seroconversion to antibody to HBeAg (anti-HBe). HBeAg-negative chronic hepatitis B infection is characterized by intermittent periods of exacerbation and quiescence. It frequently follows an aggressive disease course, with low rates of spontaneous recovery.[2-4] Epidemiologic data suggest that the median prevalence of HBeAg-negative chronic hepatitis B varies considerably, ranging from 14 percent in the United States and Northern Europe to more than 33 percent in the Mediterranean area, with an increasing prevalence worldwide.[3]

Current therapeutic options include treatment with interferon alfa, lamivudine, and adefovir dipivoxil. The goal of treatment is HBV DNA suppression, normalization of alanine aminotransferase levels, and reduction in liver necroinflammation. Longer-term objectives include the prevention of cirrhosis, end-stage liver disease, hepatocellular carcinoma, or all of these. It is unknown whether treatment can be stopped or whether long-term therapy is needed.[5]

A one-year regimen of lamivudine has been shown to achieve virologic and biochemical responses.[6-8] However, continued therapy results in resistance in approximately 20 percent of patients per year in most studies.[9] Interferon alfa and pegylated interferon have also shown efficacy; however, the durability of the response after the cessation of treatment is uncertain.[8,10-12]

In an earlier 48-week, placebo-controlled phase of this study, adefovir dipivoxil, as compared with placebo, resulted in significant histologic improvement (in 64 percent of patients vs. 33 percent, respectively), biochemical improvement (normalization of alanine aminotransferase levels, 72 percent vs. 29 percent), and virologic improvement (median reduction in HBV DNA, 3.91 log copies per milliliter [on a base-10 scale] vs. 1.35 log copies per milliliter); no resistance developed in patients treated with adefovir dipivoxil.[13,14] Here, we report the outcomes associated with stopping or continuing treatment with adefovir dipivoxil during a second 48-week randomized, controlled period; we also provide long-term data on treatment with this agent over 144 weeks.

METHODS

Between January 10 and June 7, 2000, 185 patients were enrolled and 184 treated in this international, multicenter, prospective, double-blind, placebo-controlled trial. Patients were randomly assigned to receive 10 mg of adefovir dipivoxil or placebo orally once daily for 48 weeks in a ratio of 2:1. After week 48, 123 patients who had been assigned to adefovir dipivoxil were randomly assigned either to continue with adefovir dipivoxil (the continued-adefovir group; 80 patients) or to switch to placebo (the adefovir–placebo group; 40 patients) for an additional 48 weeks. Three patients did not receive treatment during the second 48 weeks. Of the 61 patients who initially received placebo, 60 received adefovir dipivoxil in this second 48-week period (the placebo–adefovir group). Patients who received adefovir dipivoxil in the second 48 weeks were eligible to continue treatment until week 240.

Liver biopsies were required within six months or immediately before treatment and at week 48. A liver biopsy was optional at weeks 96 and 144. Serum HBV DNA and alanine aminotransferase were measured and blood chemistry assessments were conducted every 4 weeks until week 96 and then every 12 weeks.

Clinical data were monitored and entered into a database by Quintiles, a contract research organization. A central reference laboratory (Covance Laboratories) assessed all laboratory data. Gilead Sciences held all data and conducted the statistical analyses. The academic investigators had full access to the data. Each author contributed to the study design, the interpretation of the results, and the drafts and revisions of the manuscript; all authors had input into and approved the final manuscript. Drs. Hadziyannis, Tassopoulos, Heathcote, Chang, Kitis, Rizzetto, Marcellin, Lim, and Goodman vouch for the veracity and completeness of the data and the data analysis. The study was conducted in compliance with the 1975 Declaration of Helsinki and approved by local regulatory bodies. All patients provided written informed consent.

PATIENTS

Full inclusion criteria have been described previously.[13] Key criteria included HBeAg-negative, anti-HBeAg–positive status and the presence of compensated liver disease, detectable hepatitis B surface antigen (HBsAg) for at least six months, a serum HBV DNA level of at least 100,000 copies per milliliter on polymerase chain reaction (as measured with the Roche Amplicor Monitor; lower limit of detection, 1000 copies per milliliter, previously 400 copies per milliliter[13]), and a serum alanine aminotransferase level between 1.5 and 15 times the upper limit of normal.

ASSESSMENT OF EFFICACY

Primary efficacy end points were the changes from baseline in serum HBV DNA and alanine aminotransferase levels at week 96. Other efficacy end points included the percentage of patients in whom HBV DNA fell below the limit of detection of the assay, the percentage in whom alanine aminotransferase levels returned to normal, and the percentage in whom there was HBsAg seroconversion (i.e., loss of HBsAg and gain of antibody to HBsAg). End points were evaluated at weeks 96 and 144. In a subgroup of patients, histologic features of liver specimens were evaluated by an independent histopathologist (with the use of both Knodell and Ishak scoring systems, which evaluate necroinflammation and liver fibrosis on scales of 0 to 22 [Knodell] and 0 to 24 [Ishak], with higher scores indicating greater severity) who was blinded to patients' treatment assignments and the date on which the biopsy specimens were obtained.[15] Ranked assessment of inflammation and fibrosis was also performed, with severity delineated as improved, no change, or worse as compared with the baseline scores.

ASSESSMENT OF SAFETY

Safety was assessed with the use of laboratory tests and by the reported occurrence of adverse events every 4 weeks for the first 96 weeks and then every 12 weeks. All patients who received at least one dose of adefovir dipivoxil were included in the safety analysis.

RESISTANCE SURVEILLANCE

Genotypic analyses of HBV DNA polymerase mutations were performed on serum samples from patients with HBV DNA levels of more than 1000 copies per milliliter in the 123, 134, and 70 patients who received adefovir dipivoxil through weeks 48, 96, and 144, respectively. The HBV reverse transcriptase (rt) domain (amino acids rt1 to rt344) was sequenced. Sequences at baseline and after baseline were aligned with the use of the MegAlign program (DNAStar).

STATISTICAL ANALYSIS

Statistical analyses included all patients who received at least one dose of the study drug in the second 48 weeks. All HBV DNA values less than the lower limit of detection (1000 copies per milliliter) were assigned a value of 999 copies per milliliter. All tests for significance and resulting P values were two-sided, with a level of significance of 0.05.

RESULTS

CHARACTERISTICS OF THE PATIENTS

A total of 180 patients were randomly assigned to receive treatment in the second 48 weeks of the study. Of these patients, 79 continued to receive adefovir dipivoxil, 40 initially assigned to adefovir dipivoxil received placebo, and 60 were switched from placebo to adefovir dipivoxil. One patient who had been randomly assigned to the adefovir dipivoxil group withdrew from the study before taking medication in the second 48 weeks. At week 96, 125 patients continued to receive adefovir dipivoxil — 70 in the continued-adefovir group and 55 in the placebo–adefovir group. Data are reported up to week 144 for patients who received adefovir dipivoxil from baseline. Baseline demographic characteristics and those related to hepatitis B infection were not statistically different among the three groups (Table 1).

VIROLOGIC RESPONSE

At week 96, serum HBV DNA levels had decreased by a median of 3.47 log copies per milliliter in the continued-adefovir group, as compared with 1.09 log copies per milliliter in the adefovir–placebo group ($P<0.001$) (Table 2). Undetectable levels of HBV DNA were reported in 71 percent of patients in the continued-adefovir group, as compared with 76 percent and 8 percent, respectively, in the placebo–adefovir and adefovir–placebo groups. There was a rapid reduction in serum HBV DNA levels in patients in the continued-adefovir group, with persistent reductions up to week 96. In contrast, the adefovir–placebo group had a rebound in serum HBV DNA levels, with a return to baseline levels within four weeks of the discontinuation of adefovir dipivoxil in the majority of patients (Fig. 1).

Table 1. Baseline Characteristics of the Patients.

Characteristic	Continued-Adefovir Group (N=79)	Adefovir–Placebo Group (N=40)	Placebo–Adefovir Group (N=60)
Age — yr			
Mean ±SD	46±10	46±9.9	46±10.2
Median	47	47	46
Range	26–65	18–64	22–65
Male sex — no. (%)	65 (82)	33 (82)	50 (83)
Race or ethnic background — no. (%)*			
White	55 (70)	26 (65)	39 (65)
Black	4 (5)	1 (2)	1 (2)
Asian	20 (25)	13 (32)	20 (33)
Weight — kg			
Mean ±SD	75±12.2	77±10.0	74±15.2
Median	75	76	74
Range	50–111	60–105	46–135
HBV DNA level — log copies/ml†			
Mean ±SD	6.87±0.86	7.03±0.78	6.91±0.94
Median	7.07	7.16	7.05
Range	3.67–8.42	5.28–8.77	4.42–8.45
Alanine aminotransferase level — IU/liter			
Mean ±SD	140±120.7	152±140.4	149±196.8
Median	98	86	99
Range	24–742	45–657	29–1459
≤ULN — no. (%)‡	7 (9)	0	2 (3)
>ULN — no. (%)	72 (91)	40 (100)	58 (97)
Positive for HBsAg — no. (%)	79 (100)	40 (100)	60 (100)
Prior medications for HBV — no. (%)§			
Interferon alfa	30 (38)	18 (45)	27 (45)
Lamivudine¶	7 (9)	3 (8)	4 (7)

* Race was self-assigned.
† Values were log-transformed with the use of a base-10 scale.
‡ ULN denotes upper limit of the normal range; for men, the level was 43 IU per liter, and for women 34 IU per liter.
§ Some patients had received more than one type of medication.
¶ Lamivudine had been used less than 12 weeks previously in these patients.

In the patients who continued adefovir dipivoxil to week 144, HBV DNA levels remained suppressed at week 144 (median reduction in HBV DNA from baseline, 3.63 log copies per milliliter). In 79 percent of these patients, serum HBV DNA levels were less than 1000 copies per milliliter at week 144.

SEROLOGIC RESPONSE

HBsAg seroconversion (i.e., the loss of HBsAg and gain of anti-HBs) occurred in two patients, one in the continued-adefovir group at week 72 and one in the placebo–adefovir group at week 68 (approximately 20 weeks after the start of adefovir dipivoxil).

BIOCHEMICAL RESPONSE

Median reductions in serum alanine aminotransferase levels at week 96 were 59 IU per liter in the continued-adefovir group, as compared with 29.5 IU per liter in the adefovir–placebo group (P=0.01), and 79.5 IU per liter in the placebo–adefovir group (Table 2). At week 96, a return to normal levels of alanine aminotransferase (upper limit of normal, 37 IU per liter for women and 43 IU per liter for men) was achieved in 73 percent of patients in the continued-adefovir group, 80 percent in the placebo–adefovir group, and 32 percent in the adefovir–placebo group. Patients in the continued-adefovir group had sustained suppression of alanine aminotransferase throughout the study. In contrast, alanine aminotransferase levels returned to pretreatment values or higher in the majority of patients in the adefovir–placebo group within eight weeks of stopping therapy. In 32.5 percent of patients, alanine aminotransferase levels rose sharply — to more than 10 times the upper limit of normal — before returning to baseline levels. None of these elevations were associated with clinical hepatic decompensation. In the patients who continued to receive adefovir dipivoxil to week 144, alanine aminotransferase levels remained suppressed, with normalization in 69 percent of patients.

HISTOLOGIC RESPONSE

A subgroup of 47 patients underwent liver biopsy at week 96. Baseline demographic and disease characteristics of these patients were similar to those of patients in the overall study population. Patients in the continued-adefovir group had a mean reduction of 4.7 points from baseline in the overall Knodell score at week 96 (Table 3) (a mean reduction of 4.4 points at week 48). Among patients in the placebo–adefovir group, there was a mean increase of 0.9 points from baseline at week 48, with a subsequent reduction after the crossover to adefovir dipivoxil of 2.4 points from baseline at week 96, a reversal of the increase observed at week 48. In the adefovir–placebo group, there was a loss of improvement at week 48, with a median reduction of 1 point from baseline at week 96.

Table 2. Virologic and Biochemical Responses at Weeks 96 and 144.*

Response	Continued-Adefovir Group		Adefovir–Placebo Group	Placebo–Adefovir Group
	Week 96 (N=79)	Week 144 (N=70)	Week 96 (N=40)	Week 96 (N=60)
Virologic				
No. of patients assessed	70	67	38	49
Change in serum HBV DNA level — log copies/ml				
Mean ±SD	−3.35±1.18	−3.42±1.27	−1.34±1.24	−3.71±1.05
Median	−3.47	−3.63	−1.09	−3.85
Interquartile range	−4.20 to −2.59	−4.23 to −3.11	−2.19 to −0.40	−4.31 to −3.18
Range	−5.42 to −0.27	−5.42 to −1.18	−4.16 to 0.87	−5.35 to 0.44
P value†	—	NA	<0.001	0.12
Serum HBV DNA level <1000 log copies/ml — no./total no. (%)	50/70 (71)	53/67 (79)	3/38 (8)	37/49 (76)
P value‡	—	NA	<0.001	0.68
Biochemical				
No. of patients assessed	71	67	38	50
Change in serum (alanine aminotransferase) level — IU/liter				
Mean ±SD	−98±118.4	−97±120.13	−63±131.0	−130±213.2
Median	−59	−54	−29.5	−79.5
Interquartile range	−115 to −27	−121 to −28	−68 to 18	−134 to −46
Range	−717 to 51	−707 to 56	−548 to 93	−1429 to 5
P value†	—	NA	0.01	0.21
Normalization of alanine aminotransferase level — no./total no. (%)§	47/64 (73)	43/62 (69)	12/38 (32)	40/50 (80)
P value‡	—	NA	<0.001	0.51

* Negative values indicate a decrease, and positive values an increase. NA denotes not applicable.
† P values were calculated with the use of the Wilcoxon rank-sum test for the comparison between continued treatment with adefovir dipivoxil and the crossover from adefovir dipivoxil to placebo and for the comparison between continued treatment with adefovir dipivoxil and the crossover from placebo to adefovir dipivoxil at week 96. All P values are two-sided, with a level of 0.05 indicating statistical significance; there were no adjustments for multiple comparisons.
‡ Fisher's exact test was used for the comparison between continued treatment with adefovir dipivoxil and the crossover from adefovir dipivoxil to placebo and for the comparison between continued treatment with adefovir dipivoxil and the crossover from placebo to adefovir dipivoxil at week 96.
§ Patients with baseline alanine aminotransferase levels that exceeded the upper limit of the normal range were included in the analysis.

In the ranked assessment of inflammatory activity, the comparison of scores at baseline and week 96 in the continued-adefovir group showed improvement in 17 of 19 patients (89 percent) and no change in 2 of 19 patients (11 percent); in no patients did inflammation worsen. In the placebo–adefovir group, 14 of 20 patients (70 percent) had improvement, 2 of 20 (10 percent) had no change, and 4 of 20 (20 percent) had a worsening. In the adefovir–placebo group, four of eight patients (50 percent) had improvement, two of eight (25 percent) had no change, and two of eight (25 percent) had a worsening. Improvements were also seen in fibrosis, with patients in the continued-adefovir group having significant reductions from baseline in the Ishak fibrosis score at week 96 (mean [±SD] reduction, 0.63±1.07; median reduction, 1; P=0.031, as compared with the adefovir–placebo group). The improvements in fibrosis at weeks 48 and 96 were extended in patients who underwent a biopsy at week 144.

RESISTANCE PROFILE

A conserved site mutation (rtN236T) was identified in three patients in the continued-adefovir group,

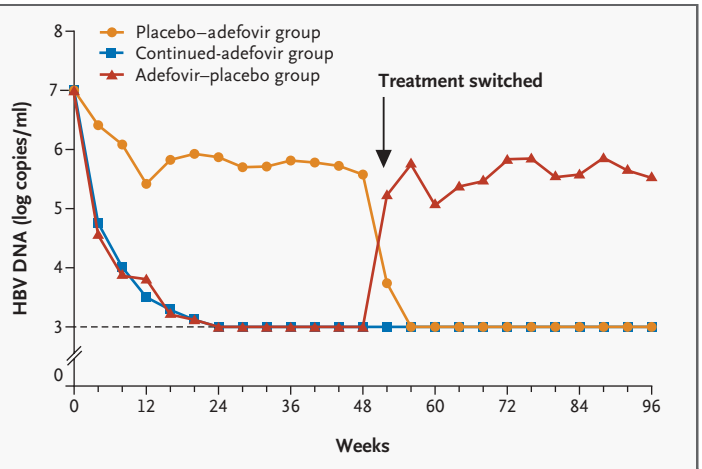

Figure 1. Median Serum HBV DNA Levels through Week 96.
The dashed line indicates 3 log copies per milliliter, which was the lower limit of detection for the assay.

two at week 96 and one at week 144. The emergence of rtN236T was associated with a rebound in serum HBV DNA and alanine aminotransferase levels. In vitro susceptibility testing demonstrated a reduction in susceptibility to adefovir that was 3.9 to 13.8 times that of wild-type virus. One patient was switched to lamivudine at week 104; HBV DNA levels, as evaluated by the Digene assay (lower limit of detection, 150,000 copies per milliliter), became undetectable, and serum alanine aminotransferase levels were normal after six months.[16] Subsequently, resistance to lamivudine developed in this patient; adefovir dipivoxil was restarted, and serum HBV DNA levels again became undetectable.

Another conserved site substitution mutation (rtA181V) in the B domain of HBV polymerase was seen in three additional patients in the continued-adefovir group, two at week 96 and one at week 144. A rebound in HBV DNA levels occurred in two of the three patients. In vitro susceptibility testing demonstrated a reduction in susceptibility that was 2.5 to 3 times that of wild-type virus. For one patient with rtA181V, lamivudine was added to ongoing adefovir therapy; serum HBV DNA levels subsequently were reduced by more than 2 log copies per milliliter.

Of the six patients in whom resistance developed, four had a reduced response to adefovir dipivoxil (serum HBV DNA reduction from baseline, <2.5 log copies per milliliter). The disease characteristics of these patients at baseline were similar to those of the overall patient population. The overall cumulative rate of resistance to adefovir dipivoxil among all patients at 48, 96, and 144 weeks was 0 percent, 3 percent, and 5.9 percent, respectively.

SAFETY

Adverse events during weeks 49 to 96 were similar in severity, nature, and frequency to those during the initial 48-week treatment period. At least one adverse event was reported in 58 of 79 patients (73 percent) in the continued-adefovir group, 41 of 60 patients (68 percent) in the placebo–adefovir group, and 32 of 40 (80 percent) in the adefovir–placebo group. The most common adverse events reported in the continued-adefovir group were headache, abdominal pain, and pharyngitis (Table 4).

The study drug was discontinued because of adverse events in two patients in the continued-adefovir group (a protocol-defined increase in serum creatinine levels of ≥0.5 mg per deciliter [44.2 μmol per liter] and hepatocellular carcinoma) and in three patients in the adefovir–placebo group (jaundice, elevated alanine aminotransferase levels, and a skin disorder).

No notable differences were seen in laboratory values from week 48, with the exception of increases in alanine aminotransferase levels associated with the withdrawal of adefovir dipivoxil therapy. In the adefovir–placebo group, 13 patients (32.5 percent) had alanine aminotransferase levels that were 10 times the upper limit of normal or higher. Elevations of alanine aminotransferase levels were observed in 6 percent of patients who continued to receive adefovir dipivoxil over 96 weeks. No patients had clinical signs of decompensation or required the intervention of an investigator. Of the 13 patients with elevations of alanine aminotransferase levels, 10 had an increase within 12 weeks after the cessation of adefovir dipivoxil therapy.

There were no overall changes in serum creatinine and phosphorus levels. Two patients in the continued-adefovir group had a confirmed increase in serum creatinine levels of 0.5 mg per deciliter or more from baseline. In one case, the highest value remained within the normal range and resolved with continued treatment. In the other case, the highest value was 2.3 mg per deciliter (203.3 μmol per liter), which returned to normal after discontinuation of the study drug. One additional patient in year 3 had a confirmed serum creatinine increase that returned to baseline within eight weeks after the cessation of adefovir dipivoxil. The safety pro-

Table 3. Changes from Baseline in Knodell Scores at Weeks 48 and 96.*

Knodell Score	Continued-Adefovir Group (N=19)		Adefovir–Placebo Group (N=8)		Placebo–Adefovir Group (N=20)	
	Week 48	Week 96	Week 48	Week 96	Week 48	Week 96
Overall						
Baseline	10.02±2.07		12.3±2.25		8.3±3.31	
Change	–4.4±2.39	–4.7±2.7	–4.3±1.49	–1.4±1.92	0.9±4.56	–2.4±4.79
Inflammation						
Baseline	8.37±1.50		10.0±1.31		6.40±2.76	
Change	–4.2±2.32	–4.3±2.71	–3.8±1.83	–0.9±1.96	0.6±3.78	–2.3±3.93
Fibrosis						
Baseline	1.84±1.17		2.3±1.39		1.9±1.17	
Change	–0.2±0.63	–0.4±1.12	–0.5±0.93	–0.5±0.93	0.3±1.17	–0.15±1.27

* Plus–minus values are means ±SD. Negative values indicate a decrease, and positive values an increase. Patients included those for whom biopsy specimens could be assessed at baseline, week 48, and week 96. Baseline values were measured before the first 48 weeks of treatment. Knodell scores (ranging from 0 to 22) evaluate necroinflammation and liver fibrosis. A lowering of scores from the initial biopsy indicates histologic improvement, and an increase indicates histologic worsening.

file over 144 weeks remained consistent with that seen earlier in the study.

DISCUSSION

As shown in other studies, treatment of HBeAg-negative chronic hepatitis B with lamivudine effectively suppresses HBV replication and results in biochemical remission and histologic improvement in more than two thirds of patients.[7,8,13] However, relapse has occurred in the majority of HBeAg-negative patients after the cessation of therapy.[8,17] Similarly, in this study, when treatment with adefovir dipivoxil was discontinued, the virologic, biochemical, and histologic benefits that had been gained in the first 48 weeks were lost. This finding suggests that because HBsAg seroconversion is rare,[2,4,11] long-term therapy will be needed in the majority of patients. Post-treatment flares in serum alanine aminotransferase levels were seen after therapy was stopped. Although these events were self-limiting in this study, it is important to monitor patients carefully after discontinuation of treatment with adefovir dipivoxil.[8,18]

To ensure a favorable risk–benefit profile, any treatment regimen must provide durable efficacy and limited toxicity, with minimal or no emergence of viral resistance. The development of viral resistance over time with the use of lamivudine, which is associated with a loss of clinical response, is common and may become serious in patients with advanced disease.[18] In another study, peginterferon therapy produced a sustained response in terms of normalization of alanine aminotransferase levels for up to 24 weeks after treatment was stopped, and 19 percent of patients had undetectable HBV DNA levels at week 24 of follow-up. However, further follow-up is required to see if this response will be sustained.[19]

Our study demonstrated that with prolonged therapy, adefovir dipivoxil brought about increasing and persistent virologic, biochemical, and histologic responses, with delayed and infrequent development of resistance. Among patients who began adefovir dipivoxil in the second 48 weeks, undetectable HBV DNA levels and normalization of alanine aminotransferase levels were achieved in a significant proportion of patients. However, comparisons of this subgroup of patients with those treated for 96 weeks should be made cautiously, since differences existed in baseline characteristics at the initiation of treatment with adefovir dipivoxil. Our results also suggest that an additional histologic benefit may occur with extended treatment, whereas cessation of treatment results in a reversal of improvement.

The adverse events associated with extended treatment with adefovir dipivoxil were similar in nature, severity, and frequency to those observed over the previous 48 weeks. Although increases in serum creatinine levels have previously been seen with

Table 4. Proportion of Patients with the Most Common Adverse Events and Renal Events.*

Event	Week 49 to Week 96			Continued-Adefovir Group	
	Continued-Adefovir Group (N=79)	Adefovir–Placebo Group (N=40)	Placebo–Adefovir Group (N=60)	Baseline to Week 96 (N=79)	Baseline to Week 144 (N=70)
	number of patients (percent)				
Any event	58 (73)	32 (80)	41 (68)	67 (85)	60 (86)
General					
Headache	12 (15)	4 (10)	5 (8)	23 (29)	19 (27)
Abdominal pain	16 (20)	7 (18)	5 (8)	22 (28)	20 (29)
Asthenia	8 (10)	6 (15)	3 (5)	15 (19)	15 (21)
Flu-like syndrome	6 (8)	4 (10)	5 (8)	14 (18)	14 (20)
Back pain	4 (5)	5 (12)	3 (5)	9 (11)	9 (13)
Pain	4 (5)	2 (5)	4 (7)	11 (14)	12 (17)
Accidental injury	4 (5)	2 (5)	2 (3)	6 (8)	8 (11)
Digestive					
Diarrhea	6 (8)	4 (10)	1 (2)	8 (10)	6 (9)
Dyspepsia	4 (5)	5 (12)†	1 (2)	7 (9)	7 (10)
Respiratory					
Pharyngitis	14 (18)	8 (20)	8 (13)	23 (29)	25 (36)
Increased cough	3 (4)	4 (10)	2 (3)	6 (8)	7 (10)
Bronchitis	2 (3)	1 (2)	1 (2)	6 (8)	9 (13)
Metabolic and nutritional					
Increased alanine aminotransferase levels	2 (3)‡	6 (15)†	1 (2)	3 (4)	3 (4)
Musculoskeletal					
Arthralgia	6 (8)	5 (13)†	1 (2)	7 (9)	6 (9)
Urogenital					
Increased creatinine levels	2 (3)	0	0	3 (4)	3 (4)
Hematuria	1 (1)	0	1 (2)	2 (3)	2 (3)
Kidney calculus	0	0	1 (2)	0	1 (1)
Kidney pain	0	0	1 (2)	2 (3)	4 (6)

* The most common adverse events are those that occurred in 10 percent or more of the patients in any treatment group.
† Fisher's exact test was used for the comparison with the placebo–adefovir group ($P<0.05$).
‡ Fisher's exact test was used for the comparison with the adefovir–placebo group ($P<0.05$).

higher daily doses (>30 mg), the risk is low with a daily dose of 10 mg.

The findings of this study raise two important questions: When should treatment be initiated, and when is it safe to stop? In view of the progressive course of HBeAg-negative chronic hepatitis B[1,3] and the progression of liver damage in patients who received placebo for 48 weeks in this study, it is reasonable to suggest that treatment should not be delayed. However, long-term therapy will be needed for the majority of patients. Therefore, there are several important factors to be weighed before treatment is begun: the patient's age, the severity of liver disease, the risk of disease progression, the risk of resistance, the likelihood of compliance, and the costs associated with long-term therapy.

Treatment with adefovir dipivoxil for 144 weeks resulted in continuing benefits in terms of viral suppression, normalization of biochemical measures, and histologic improvement. These benefits were associated with a delayed and infrequent emergence of resistance, making adefovir dipivoxil an excellent

candidate for the long-term management of HBeAg-negative chronic hepatitis B.

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APPENDIX

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